

*REMARKS/ARGUMENTS**The Pending Claims*

Claims 1-12, 15, and 16 are pending and are directed to a method of producing pluripotent stem cells.

*Amendments to the Claims*

The claims have been amended to point out more particularly and claim more distinctly the invention. In particular, claim 1 has been amended to clarify that the testis cells are derived from a postnatal mammal, as supported by original claims 13 and 14 (now canceled). No new matter has been added by way of the amendments to the claims.

*Summary of the Office Action*

The Office rejects claims 1-16 under 35 U.S.C. § 103(a) as allegedly unpatentable over two or more of the following: (a) Nagano et al., *Biology of Reproduction*, 68: 2207-2214 (2003), (b) Matsui et al., *Cell*, 70(5): 841-847 (1992), (c) Beumer et al., *Cell Death and Differentiation*, 5: 669-677 (1998), (d) Meng et al., *Science*, 287: 1489-1493 (2000), (e) Donovan et al., *Current Opinion in Genetics & Development*, 13: 436-471 (2003), (f) Kanatsu-Shinohara et al., *Biology of Reproduction*, 70: 70-75 (2004), and (g) Shinohara et al., *Proc. Natl. Acad. Sci. USA*, 96: 5504-5509 (1999).

The Office provisionally rejects claims 1-6 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-7 and 12 of co-pending U.S. Patent Application No. 10/553,118.

Reconsideration of the rejections is hereby requested.

*Discussion of the Obviousness Rejections*

The Office contends that it would have been obvious to one of ordinary skill in the art to add an isolation step as suggested in Matsui et al. to the culturing method of Nagano et al. in order to arrive at the inventive method. The Office relies on the remaining cited references to provide the features of the remaining dependent claims. The obviousness rejections are traversed for the following reasons.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned *Graham* factors here indicates that the present invention, as defined by the pending claims, is unobvious in view of the cited references.

As regards the scope and content of the prior art, Nagano et al. teaches culturing testis cells (e.g., spermatogonial stem cells and germ cells) from transgenic mice that express lacZ using a medium containing GDNF, LIF, bFGF, and feeder cells. The Office acknowledges that Nagano et al. does not teach isolating pluripotent stem cells from the spermatogonial stem cells. However, the Office contends that it would have been obvious for one of ordinary skill in the art to isolate pluripotent stem cells from the spermatogonial stem cells of Nagano et al., since Matsui et al. suggests that isolated pluripotent embryonic stem cells from murine primordial germ cells in culture could be maintained on feeder layers. The Office relies on the remaining cited references to provide the features of the remaining dependent claims.

For purposes of the analysis here, and for the sake of argument, the level of ordinary skill can be considered to be relatively high, such that a person of ordinary skill in the art would have an advanced degree and/or several years of experience in the relevant field.

The present invention, as defined by the pending claims is directed to a method of producing pluripotent stem cells, which comprises culturing testis cells using a medium containing GDNF or an equivalent thereto, wherein the testis cells contain spermatogonial stem cells, and wherein the testis cells are derived from a postnatal mammal, and isolating pluripotent stem cells from the cultured testis cells.

Before the discovery of the inventive method, one of ordinary skill in the art believed that it was impossible to establish pluripotent stem cells from postnatal germ cells. For example, Labosky et al. (*Development*, 12: 3197-3204 (1994); copy enclosed herewith) reports that pluripotent cell lines can be established from primordial germ cells of 8 days post coitum (p.c.) embryos and 12.5 days p.c. genital ridges; however, germ cells from the gonads of 15.5 days p.c. embryos and newborn mice did not give rise to embryonic germ cell lines under the conditions disclosed in the prior art (see, e.g., page 3199, paragraph bridging columns 1 and 2). Matsui et al. does not teach the derivation of pluripotent stem cells from postnatal primordial germ cells. Therefore, one of ordinary skill in the art would not have had any reason to use the methodology of Matsui et al. for the isolation of pluripotent stem cells from the postnatal cultured testis system of Nagano et al. Furthermore, none of the remaining cited references provides any reason to combine the isolation method of Matsui et al. with the culturing method of Nagano et al. In view of the teachings of the prior art as exemplified by Labosky et al., one of ordinary skill in the art would not have been motivated to isolate and expand a culture of pluripotent stem cells from postnatal testis cells, as required by the pending claims, nor would one of ordinary skill in the art have reasonably expected such an approach to be successful.

Furthermore, Applicants note that the Office relies on Beumer et al. to provide the teaching of p53-deficient testis cells. Beumer et al. teaches that spermatogenesis (production of mature spermatogonia from undifferentiated spermatogonia) is more efficient in p53 knock-out mice; however, the production of spermatogonia is completely different from the production of pluripotent stem cells, which is the subject matter of the pending claims. As a result, one of ordinary skill in the art would not have reasonably expected the production of pluripotent stem cells to be similar to that of spermatogonia, and there would be no reason for one of ordinary skill in the art to combine the teachings of Beumer et al. with that of the other cited references regarding pluripotent stem cells.

The inventors recognized that pluripotent stem cells could be established from postnatal mammals without destruction of embryos or genetic modification using the inventive method. The inventive method circumvents the ethical problem of destroying embryos in the production of pluripotent stem cells, which is surprising and unexpected in view of the methods disclosed in the prior art (see, e.g., Labosky et al.).

Considering all of the *Graham* factors together, it is clear that the present invention – as defined by the pending claims – would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combined disclosures of the cited references. Accordingly, the obviousness rejection should be withdrawn.

*Discussion of the Provisional Nonstatutory Obviousness-Type Double Patenting Rejection*


The Office contends that claims 1-6 are unpatentable over claims 1-7 and 12 of U.S. Patent Application No. 10/553,118 (“the ‘118 application.”) This rejection is traversed for the following reasons.

Claim 1 and, thus, claims 2-6 dependent thereon of the present application have been amended to include the features of claims 13 and 14, which recite that the testis cells are derived from a postnatal mammal. Applicants note that claims 13 and 14 were *not* included in the provisional nonstatutory obviousness-type double patenting rejection in view of U.S. Patent Application No. 10/553,118 since claims 1-7 and 12 of the ‘118 application do not teach or suggest the production of pluripotent stem cells from postnatal testis cells and the isolation of the pluripotent stem cells from cultured postnatal testis cells. Accordingly, the provisional nonstatutory obviousness-type double patenting rejection has been rendered moot, and Applicants request that the provisional nonstatutory obviousness-type double patenting rejection be withdrawn.

*Conclusion*

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

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